

CLINICAL REPORT

# Ectrodactyly-ectodermal dysplasia-clefting syndrome presenting with bilateral choanal atresia and rectal stenosis

Alexandra J. Childs<sup>1,2</sup>  | David C. Mabin<sup>1</sup> | Peter D. Turnpenny<sup>3</sup>

<sup>1</sup>Department of Paediatrics, Royal Devon and Exeter NHS Foundation Trust, Exeter, UK

<sup>2</sup>University of Exeter, Exeter, UK

<sup>3</sup>Clinical Genetics, Royal Devon & Exeter NHS Foundation Trust, Exeter, UK

## Correspondence

Alexandra J. Childs, Department of Paediatrics, Royal Devon and Exeter Hospital, Barrack Road, Exeter EX2 5DW, UK.  
Email: alexandrachilds@nhs.net

## Abstract

We present the case of a male who shortly after birth developed acute respiratory distress due to bilateral choanal atresia, following which he was found to have rectal stenosis. Genetic testing for CHARGE syndrome was negative, but whole genome sequencing identified heterozygosity for a pathogenic missense variant in *TP63* (c.727C > T, p.(Arg243Trp)). He also has partial cutaneous syndactyly of the third and fourth fingers of the right hand, and bilateral lacrimal duct stenosis/aplasia. A later maxillofacial review identified a palpable submucous cleft and his scalp hair is blond and slightly sparse. Choanal atresia and rectal stenosis are recognized features of ectrodactyly-ectodermal dysplasia-clefting syndrome, but we believe this is the first report of a case presenting with these features in the absence of the cardinal features.

## KEYWORDS

choanal atresia, ectrodactyly-ectodermal dysplasia-clefting syndrome, EEC syndrome, rectal stenosis, *TP63*

## 1 | INTRODUCTION

Ectrodactyly-ectodermal dysplasia-clefting (EEC; OMIM 604292) is a rare pleiotropic condition following autosomal dominant inheritance due to heterozygous pathogenic variants in the *TP63* gene. The cardinal features are ectrodactyly (split-hand-foot malformation), ectodermal features affecting the skin, hair, teeth and nails, and oral clefting of the lip and palate. Also reported are: blocked or absent lacrimal duct, blepharophimosis, syndactyly, conductive hearing loss, cloudy cornea, cataract and glaucoma, dysplastic kidneys and dilated urethra, endocrine abnormalities affecting the pituitary and thyroid, choanal atresia and anal stenosis/atresia. Variants in the *TP63* gene are reported in ~93% of patients with a clinical diagnosis of EEC syndrome (van Bokhoven et al., 2001). The *TP63* gene encodes a sequence-specific transcription factor, influencing the development of the human embryonic endoderm by involvement in epithelial, limb and craniofacial development (van Bokhoven, Melino, Candi, & Declercq, 2011). At least six

different transcripts of *TP63* have been identified, generated from two different promotor genes with additional alternative splicing resulting in three different C-termini (Yang et al., 1998). Several EEC-like syndromes have been described, of which five are also caused by variants in *TP63*: Ankyloblepharon-Ectodermal defects-Cleft lip/palate (OMIM 106260); Limb Mammary Syndrome (OMIM 603543); Acro-Dermato-Ungual-Lacrimal-Tooth syndrome (OMIM103285); Rapp-Hodgkin Syndrome (OMIM 129400); and non-syndromic Split Hand/Foot Malformation (SHFM) (OMIM 605289) (Rinne, Hamel, van Bokhoven, & Brunner, 2006). There is significant clinical overlap in these conditions with the core features being split-hand-foot malformation, oral clefting, and ectodermal dysplasia.

We report a patient presenting soon after birth with bilateral choanal atresia followed by rectal stenosis. Ectodermal features emerged only later, and we believe this is the first report of a patient with EEC syndrome presenting with this combination of anomalies in the absence of cardinal features.

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## 2 | CASE PRESENTATION

Our male patient was born at 35 + 6 weeks gestation, weight 2,093 g, via spontaneous vaginal delivery. His mother had symphysis pubis dysfunction but an otherwise uncomplicated pregnancy. She was para 2 gravida 1, with a previous healthy infant born at 34 + 5 weeks gestation. The 20-week anomaly scan suggested a small-for-dates fetus, though otherwise unremarkable and fetal growth was monitored by serial scans. He was born in good condition initially with appearance, pulse, grimace, activity and respiration (APGAR) scores of 5<sup>1</sup>, 7<sup>5</sup>, and 10<sup>10</sup>. Subsequently, he quickly developed significant respiratory distress with high oxygen requirements, despite commencing noninvasive ventilation. Clinicians were unable to pass a nasogastric tube through either nasal passage. He was diagnosed with bilateral choanal atresia and intubated, ventilated, and transferred for surgery.

By Day 3, he had not opened his bowels and was found to have rectal stenosis. Therefore, on Day 4 of life, he underwent both anoplasty and choanal atresia repair under anesthetic. An echocardiogram showed a heart with normal morphology and a small patent foramen ovale. There were no abnormalities identified on either abdominal, renal or spinal ultrasound scans. Soon after birth, he was noted to have watery, sticky eyes. Once established on a combination of oral and orogastric tube feeds, he was discharged home. He required twice daily rectal dilatations, performed by his parents until 1 year of age.

He was followed up in the community with input from speech and language therapy for his swallow, requiring specialized teats and thickened fluids. During infancy, he suffered recurrent lower respiratory tract infections leading to prophylactic antibiotic cover. At 1 year of age, he had a normal microlaryngoscopy and bronchoscopy and visual examination of the soft palate. However, he had a palpable submucous cleft. He required medication for gastroesophageal reflux. At 23 months of age, due to persistent sticky eyes, he was reviewed by ophthalmology who identified blocked lacrimal ducts. At 3 years of age, these continued to require dilatations and stents in situ.

At 1 year of age, he also underwent unilateral orchidopexy for a right undescended testis. At 3 years, he continues to have small stature, tracking along just below the 0.4th height centile. Apart from a perianal abscess requiring drainage in the second year of life, he has needed no further rectal procedures.

## 3 | MATERIAL AND METHODS

Clinical genetic input at the initial point of discharge following the neonatal period found the features as mentioned: short stature, choanal atresia, rectal stenosis, poor swallow and sticky eyes, as well as the presence of a partial cutaneous syndactyly between the third and fourth digits of his right hand (Figure 1). Chromosomal microarray and sequencing of the *CHD7* gene for CHARGE syndrome yielded normal results. It was decided to recruit him to the 100,000 Genomes Project rather than sequence a panel of relatively minor genes linked to the CHARGE syndrome phenotype. Whole genome sequencing



**FIGURE 1** Partial cutaneous syndactyly of digits 3–4 of the right hand, identified soon after birth (photograph at 13 months of age) [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

identified a heterozygous missense variant in exon 5 of *TP63* (c.727C > T) resulting in the amino acid substitution p.(Arg243Trp). This variant has previously been reported in association with both EEC and ADULT syndrome (Celli et al., 1999; Yang, Lin, Zhu, Luo, & Lin, 2018) and is not listed in population databases, including gnomAD (Karczewski et al., 2019). At this stage, he was 13 months old and a clinical review revealed light colored, relatively sparse scalp hair, mild malar hypoplasia (Figure 2) and dystrophic, pitted nails. The *TP63* variant was confirmed by Sanger sequencing and was de novo, with neither parent showing similar clinical features.

## 4 | EDITORIAL POLICIES AND ETHICAL CONSIDERATIONS

Full informed consent was obtained from the mother of our patient for this manuscript and the photographs included as figures.

## 5 | DISCUSSION

Most *TP63* variants causing EEC are reported as missense or frame-shift in exons 13 and 14, with reports in the literature of nonsense (Eisenkraft et al., 2015), small deletions (Giampietro, Baker, Basehore, Jones, & Seroogy, 2013), one report of a large intragenic deletion

(Aradhya et al., 2012) and splice site variants (Kantaputra, Matangkasombut, & Sripathomsawat, 2012). There are at least 23 identified pathogenic variants within the *TP63* gene, which are associated with EEC (Rinne et al., 2006). The large majority of the



**FIGURE 2** Pictured at 13 months of age, showing sparse scalp hair [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

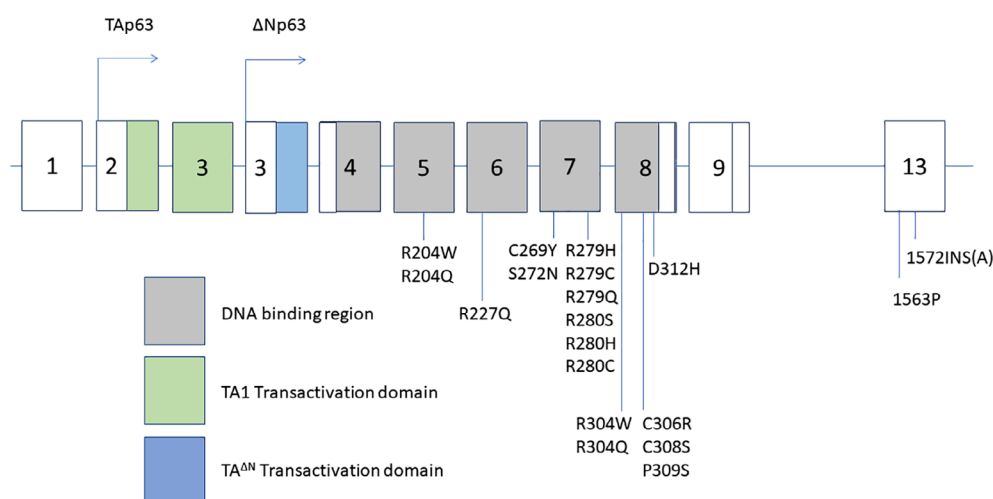
reported variants are in the DNA-binding (Figure 3) region, and only two published which are located outside this region (Celli et al., 1999; Rinne et al., 2006). Variants that disrupt the DNA-binding capacity result in reduced transcription (Celli et al., 1999). The variant found in our patient was previously reported in a Japanese patient who presented with ectrodactyly and bilateral cleft lip and palate, with a father determined to be mosaic (Kosaki et al., 2008).

Wide phenotypic variation seen with *TP63* variants has been well documented (Celli et al., 1999; Clements, Techanukul, Coman, Mellerio, & McGrath, 2010), with a recent report of molecularly confirmed monozygotic twins showing discordance of classic EEC syndrome features, that is, cleft palate and hand malformations, but not nonclassical, that is, choanal atresia (Wenger et al., 2018).

In this patient, the cardinal features of EEC, in the form of ectodermal anomalies and submucous cleft palate were apparent only after infancy, and partial cutaneous syndactyly observed in the newborn period, did not lead to a suspicion of EEC syndrome.

From more than 230 published cases only 16% do not present with ectrodactyly, 77% have ectodermal dysplasia, and clefts are present in 68% (Augello, Berg, Muller, & Schwenger-Zimmerer, 2015). The latter two features only became apparent in our patient after infancy. Although there are multiple reports of EEC syndrome without ectrodactyly, we are unaware of a case presenting with the combination of bilateral choanal atresia and rectal atresia.

Previous reports of choanal atresia occurring in EEC syndrome have been in the context of more obvious cardinal features or a positive family history (Christodoulou, McDougall, & Sheffield, 1989; Slavotinek & Clayton-Smith, 1999; Tucker & Lipson, 1990). Two of these published reports highlight probands with a similar phenotype to our patient, that is, with choanal atresia without ectrodactyly, but with other features such as polydactyly and obvious clefting.



**FIGURE 3** Schematic diagram illustrating the intron-exon structure of the *TP63* gene with the DNA binding region highlighted. The two different transcriptional start sites are illustrated leading to the six different isoforms as described by Yang et al. (1998). Nineteen previously published variants associated with EEC are illustrated including the non-DNA binding variation on exon 13 as reported by Celli et al. (1999), though only seen in the  $\alpha$  isoform and that reported by Rinne et al. (2006). The variant in our patient (c.727 C > T) is listed as R204W as documented in the original publication [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

All the previous reports of rectal abnormalities occurring as part of EEC syndrome (Celik et al., 2011; De Smet & Fryns, 1995; Majewski & Goecke, 1996) have included ectrodactyly, except for one report of a child who presented with extensive ectodermal defects, dysmorphic facial features and anal atresia, and later was found to have unilateral choanal atresia (Ruml, Cuturilo, Lukac, & Peters, 2015). There is one other published report of anal abnormalities in conjunction with ectrodactyly within a Chinese family with a *TP63* variant; however, these cases had none of the hallmarks of ectodermal dysplasia or palatal abnormalities (Su, Yuan, Huang, Wang, & Zhang, 2013). Our case further highlights the variability of EEC syndrome and the phenotypic diversity associated with *TP63* variants. This diagnosis and gene should be considered when an infant presents with choanal atresia and/or rectal stenosis, even when the classic features of EEC are not evident in infancy.

## 6 | CONCLUSION

This case further highlights the variability of EEC syndrome and the phenotypic diversity associated with *TP63* variants, as well as the need to consider this diagnosis when an infant presents with choanal atresia and/or rectal stenosis. Next generation sequencing was helpful in securing the diagnosis.

## ACKNOWLEDGMENTS

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## CONFLICT OF INTEREST

Regarding the manuscript "EEC syndrome presenting with bilateral choanal atresia and rectal stenosis," no author or contributor stated any conflicts of interest.

## DATA AVAILABILITY

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

## ORCID

Alexandra J. Childs  <https://orcid.org/0000-0002-5534-9635>

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